A Review On Penetration Enhancer For Transdermal Patches

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Abstract- *The transdermal system is one of the route of drug administration that deliver drugs through the skin . Transdermal patches are most convenient in the transdermal delivery system. And ,it has various advantages in conventional route . Unfortunately , stratum corneum is the skin outer most layer act as a barrier that prevent entrance of exogenous molecule . To overcome the this problem various type of the penetration enhancers are discovered to improve the delivery of drugs through the skin. Despite , the pharmaceutical industries are using particular physical and chemical penetration enhancer in trandermal products. In this article , I have discussed about the permeation enhancement technology for trandermal drug delivery as well as the mechanism of action*

Keywords- Transdermal, Drug delivery, penetration, skin, stratum corneum .

I. INTRODUCTION

Alongside around 40% of the medication delivery market, transdermal route now ranks with oral treatment as the most successful novel research area in drug delivery. Candidate transdermal or dermal system products are being evaluated in clinical settings. A lidocaine patch will soon be released, and the global transdermal patch industry is expected to reach two billion pounds thanks to medications including nicotine, nitroglycerin, clonidine, oestrogen, testosterone, and fentanyl. A dermatological medicine's capacity to penetrate skin in sufficient amounts to have the desired therapeutic effect is crucial to the treatment's efficacy when utilised for systemic drug delivery. There are numerous causes for improper transdermal medication administration. First off, aside from minor lipophilic compounds, the skin is a great permeability barrier**.** Furthermore, unless one compromises the protective skin barrier function, achieving high and constant drug flux through the skin is a difficult task with a low probability of success.

TRANSDERMAL DRUG DELIVERY SYSTEM :

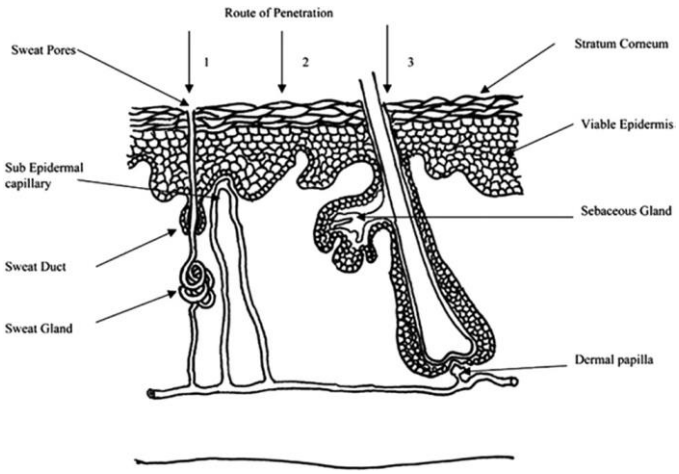
TDD is a painless method of systemic drug delivery that involves applying a drug formulation to healthy, undamaged skin. The stratum corneum is first penetrated by the medication, which then moves into the deeper epidermis and dermis without accumulating in the dermal layer.

SKIN PERMEATION ENHANCERS :

The skin permeation enhancers are used to promote the drug transport through the skin barriers . It increases the content of the water molecules between the bilayer which which increases the diffusion of the polar drugs across the skin layer . the therapeutic concentration of the drug in the blood can be achieved and maintained by minimizing the resistance offered by the dead skin layer , that is the stratum in corneum to allow the drug to penetrate to cross the skin bilayer and reach the systemic circulation.

MECHANISAM OF ACTION :

Three possible routes exist for drug molecules in contact with the skin's surface to enter the body: directly across the stratum corneum, through the sweat ducts, and through the hair follicles and sebaceous glands (together known as the shunt or appendageal route). Scientists have argued over the years over the relative relevance of the shunt or appendageal route in comparison to transport across the stratum corneum, which is further confounded by the absence of an appropriate experimental model to allow separation of the three paths.



Simplified representation of skin showing routes of penetration:

1 .Through the sweat ducts;
2. Directly across the stratum corneum;
3. Via the hair follicles

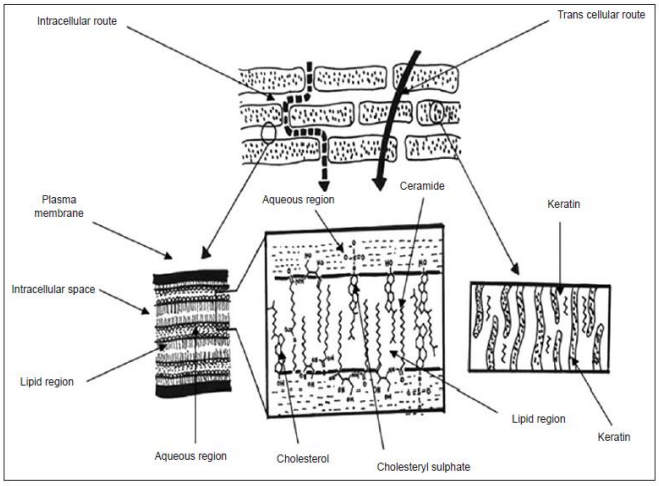
TECHNIQUES OF ENHANCING DRUG PERMEATION THROUGH THE SKIN :

There are certain novel method and techniques , by which the penetration of the drug molecule can be enhanced . The recent techniques that have been employed to increase the skin permeation includes

- ❖ Physical Technique
- ❖ Chemical techniques

PHYSICAL TECHIQUES :

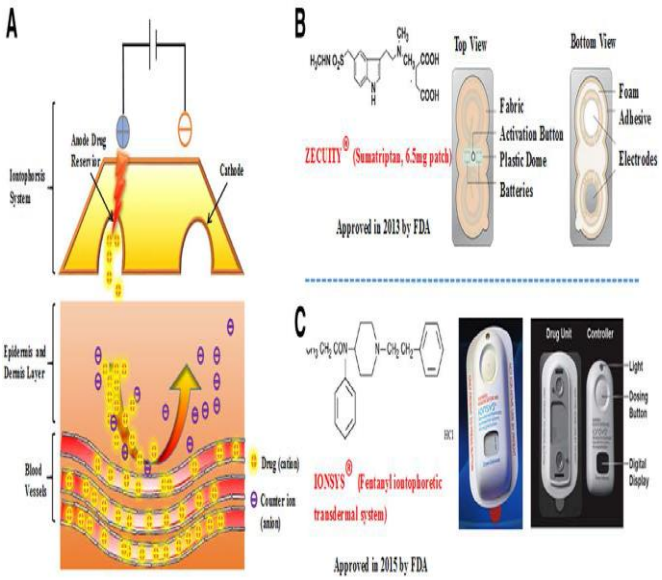
There are a variety of ways to get beyond the stratum corneum barrier function, including chemical boosters, fresh formulations, and physical development methods. Azone and cyclodextrins are two chemical penetrators that have been created to enhance medicine skin penetration. However, in addition to their ineffectiveness in improving transdermal penetration, they are also linked to adverse effects such redness, irritation, and hypersensitivity. As a result, cutting-edge formulations like nanoparticles, liposomes, transferosomes, microemulsion, hydrogels, invasomes, and ethomes have been created to enhance transdermal absorption. With the rapid development of technologies like microelectromechanical systems, artificial intelligence, microneedles, sonophoresis, iontophoresis, electroporation, microwave, magnetophoresis, and lasers, physical penetration technologies have also advanced. To improve transdermal absorption, they can directly and permanently alter the skin's surface structure.



Diagrammatic representation of the stratum corneum and theintercellular and transcellular routes of penetration

IONTOPHORESIS:

Using a little amount of electric current on a drug reservoir located on the skin's surface, this approach increases the medication's ability to permeate the skin. To help the medication pass the skin bilayer, a 0.5 ampere/cm2 electric current is permitted to circulate in the drug reservoir. To improve the penetration of cyanide and strychnine across the rabbit's skin, Lutec invented this invivo approach at the beginning of the 20th century. This method uses two electrodes in two chambers that are put on the skin's surface. A steady electric current flow ensures controlled drug administration, and the amount of drug that permeates the skin is exactly proportional to the amount of current flowing through the device. The Iontophoresis device's electric current flow ensures dosage accuracy.



Iontophoresis for transdermal permeation.

(A) The principle of iontophoresis using an Ag/AgCl electrode system.
(B) (B), (C) Commercial formulationsusing iontophoresis. A− = anionic drugs, Cl− = chloride ions in the drug reservoir, D+ = cationic drugs, FDA = Food and Drug Administration, Na+ = sodium ionsin the drug reservoir.

The sole drawback of iontophoresis is that it can result in localised erythema at the application site. The Alza Corporation's E-Trans device, which is designed to administer medications both locally and systemically, is one of many

iontophoretic devices that have been employed for transdermal drug delivery. WEDD (Wearable electronic disposable drug delivery), another iontophoretic device, has the benefit of supplying changeable voltage, which allows the dose of the medicine to be adjusted appropriately. Birch Point Medical Incorporation is the company that created this apparatus.

ULTRASOUND/PHONOPHORESIS / SONOPHORESIS:

The sound waves of frequency ranging from 20 KH_Z to 1 MK_Z with intensity of 1 to 3 W/cm^2 refers to the ultra sound waves . The phenomenon of enhancement in the permeation of the drugs transdermal route by ultrasound waves is known as sonophoresis or phonophoresis . Ultrasound technique as been used to enhance the permeability of high molecular weight drugs like heparin, insulin, hormone etc. The ultrasound waves enhance delivery by various mechanism

CAVITATION :

Cavitation is the process of forming a gaseous bubble as a result of pressure changes brought on by ultrasound. Cavitation also causes the bubble to move in an ultrasonic field in a slow oscillatory manner. The cavitation-induced collapse of the results in shock waves that alter the structure of the tissue, particularly the stratum corneum, enhancing medication permeability.

THERMAL EFFECTS :

The ultrasound device's generation of ultrasonic waves raises the medium's temperature, aiding in the opening of pores and causing some lipid breakdown in the surrounding tissue, which improves the drug's penetration into the skin.

CONVECTIVE TRANSPORT :

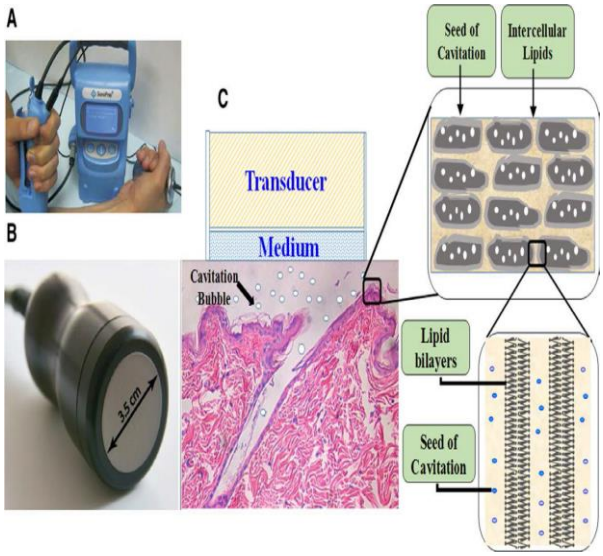
The interference or disturbance in the event and the reflected ultrasound in the diffusion cell lead to convective transport, which increases the penetration of drugs through pores like hair follicles and sweat ducts.

ADVANTAGES :

1. Enhanced drug penetration over passive transport.
2. Skin remain intact, therefore low risk of introducing infection.
3. Less risk of systemic absorption than injection.

DISADVANTAGES :

1. It can be time consuming to administer .
2. SC must be intact for effective drug penetration.

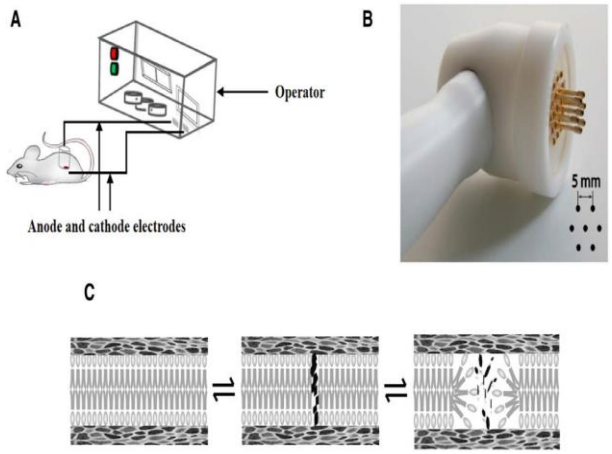


Sonophoresis for transdermal permeation.

(A) Low-frequency ultrasound treatment in a clinical setting with the SonoPrep® device (Echo Therapeutics,Franklin, MA).
(B) Ultrasound transducer, 3.5-cm diameter.
(C) (C) Mechanistic overview of sonophoresis-facilitated drug delivery

ELECTROPORATION:

Electroporation involve the use of voltages in the range of 30 to 100 volts for the duration of 10 mSec to 100 mSec. The voltage applied make reversible pores in the membrane of the skin. Electroporation from the last two decades have been extensively used in various field including gene therapy, RNA transfer, protein delivery and introducing nucleotides and antibodies in the cells. Now a days it is widely used in drug delivery through the transdermal routes. The rate and amount of penetrant passed through the skin is proportional to the quantity and the duration of pulse voltage applied. The electroporation has been used to deliver physostigmine for the organophosphate poisoning.

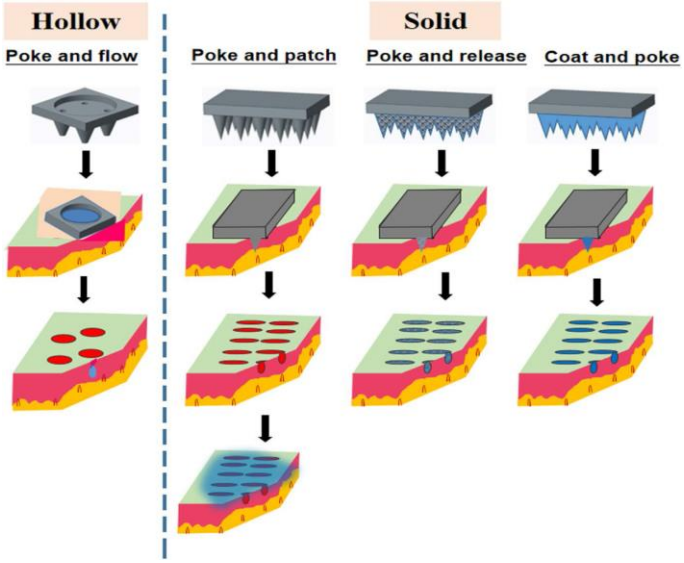


Electroporation for transdermal permeation.

(A) The components of an electroporation device.
(B) (B) Electroporation pin electrodes arranged in a honeycombconfiguration.
(C) Mechanistic overview of electroporation facilitated drug delivery.

MICRONEEDLES :

Microneedles because of micron size are responsible for painless delivery of drugs. It is injected in an array to a particular area of the skin surface there by creating holes and the transport is hence facilitated across the skin. Microneedles are fabricated from various metals, silicon and even plastics. Microneedles of smaller size are even being used to deliver therapeutic agent into the particular cells. The releasing patterns of choice and accurate dosing can be achieved by using microneedles technology.insulin has been widely studied for the pain free delivery through microneedles technology.



Schematic illustration of hollow and solid microneedles

THERMAL PORATION :

Thermal poration is a technique that speeds up medication penetration by heating the skin's stratum corneum and surrounding tissues to create pores. For less than a second, the skin is exposed to temperatures greater than 100^0C. The skin becomes significantly more permeable when exposed to such temperatures without suffering any significant skin damage. The greater temperature enhances the permeability of the medications by different mechanism which include developing holes in the stratum corneum, including vascular permeability so that drug enters straight in to the blood circulation.

RADIO FREQUNCY:

Radio frequency is comparatively a novel transdermal drug delivery technique . In this method an array of microelectrodes usally 100 / cm2 are applied to the skin surface . The radio frequency produced cause disruption of the layer of the skin . It depends upon the frequency of the ratio waves applied which determine how deep the ablation of skin is caused . Ratio frequency enhances the delivery of drug across the skin by creating micro channels in the stratum corneum . Pretreatment of clean shaved rat skin has shown significant increace in the permeability of drugs like diclofenac and granisetron . In human skin it has successfully been used to deliver testosterone , diclofenac sodium and human growth hormone

JET PROPELLED PARTICULATE DELIVERY:

This method uses high-velocity (100 ms-1) compressed inert/nobel gas jets that are primarily helium. Transdermal jet injectors carry a medication and inert gas mixture in a cartridge that is shot into the skin quickly through the nozzle of the device. This acceleration jet opens up the stratum corneum, which improves the penetration of the medication via the skin. Although many different medications have been utilised using this strategy, inulin is the first pharmacological molecule to do so. DNA, vaccinations, protein, midazolam, and lidocaine are among the others.

SUPER SATURATION :

Although not frequently utilised, super saturation has been successfully tested with in situ models. The method uses a supersaturated drug solution in the medium to increase the penetrant's thermodynamic activity above unity. The penetrant's thermodynamic activity acts as the propulsion for it to penetrate the skin layer. The in vitro examination of a lipophilic medication on pig skin was the first application of

the super saturation technique. Other physical procedures include suction ablation, skin stretching and abrasion, skin puncture and perforation, and photomechanical waves.

MARKETED TDDS WITH PHYSICAL PENETRATION ENHANCEMENT TECHNIQUE:

S.NO.	Enhnacement method	Technology name	Manufacturer	Drug product
1	Microporation	Macroflux	Alza	Vaccines various liquid injectables medications
2	Microporation	Microstructured transdermal system (MTS)	3M	Hydrophilic large molecules
3	Needleless injectors	Powder ject	Powder Ject Pharmaceuticals, PLC	Insulin
4	Needleless injectors	Intraject	Weston Medical	Vaccines various liquid injectables medications
5	Medicated tattoos	Med-Tats	Lipper-Man Ltd	Acetaminophan vitamin C St. John's wort Echinacea
6	Heat	CHADD (controlled, heat-aided drug delivery)	Zars, Inc	5-Caine (lidocaine and tetracaine)
7	Iontophoresis	Phoressor iontophoretic drug delivery system	Iomed	Other anesthetics
8	Iontophoresis	E-Trans	Alza	Fentanyl
9	Reverse iontophoresis	GlucoWatch	Cygnus	Diagnostics
10	Phonophoresis	SonoPrep	Sontra Medical	Peptides other large molecules
11	Reverse iontophoresis	Symphony diabetic management system	Sontra Medical	Symphony diabetic management system
12	Microparticulate delivery	5MP	Atrix labs	Dapsone nucleoside analogs antifungals

CHEMICAL TECHNIQUES:

MECHANISM OF ACTION OF CHEMICAL PEENETRATION: ENHANCERS :

- Disruption and ablation of the skin lipid bilayer .
- Increase in the mobility of intercellular lipid.
- Replacement of bound water within the intercellular spaces by lipophilic drugs .
- Interction with keratin and disruption in lipid packaging
- Penetration through hair follicles and sweat ducts

CHEMICAL AGENTS AS PENETRATION ENHANCERS :

.Water
.Sulphoxides
. Azones
. Pyrrolidones
. Fatty acids
. Alcohol and glycols
. Essential oil,terpenes and terpenoid.

WATER:

Utilizing water is a crucial strategy to enhance topical and transdermal drug delivery. The human stratum corneum has a water content of between 15 and 20% of the tissue dry weight, which varies depending on the humidity of the surrounding environment. It has been discovered that the transdermal administration of both hydrophilic and lipophilic medications is directly related to hydration.

SULPHOXIDES AND SIMILAR CHEMICALS:

One of the most popular and earliest investigated penetration enhancers is dimethyl sulphoxide (DMSO). The potent aprotic solvents DMSO, Dimethyl sulphoxide (DMAC), and dimethly formamide are structurally related to one another. Idoxuridine, a commercial formulation used to treat severe herpes infections on the skin, contains DMSO as a cosolvent in a vehicle. Lidocaine, hydrocortisone, and naloxone's ability to penetrate the skin has been enhanced by the application of DMSO, DMAC, and DMF.Caffeine penetration through the skin increased by 12 times, as demonstrated by Southwell and Barry, who came to the conclusion that the membrane damage caused by DMSO was irreversible. When applied to the skin, DMSO transforms intercellular keratin into a (beta) sheet and denaturizes proteins.

AZONES:

Azones, also known as laurocapram or 1-dodecylazacycloheptan-2-one, are cyclic amide-alkylsulphoxide pyrrolidone structures that lack the aprotic group of sulphoxide. With a logpoctanol/water ratio of 6.2, azone is a highly lipophilic molecule that is compatible with and soluble in the majority of organic solvents, including alcohols and propylene glycol. Azone has very little pharmacological activity, very low toxicity, and minimal irritancy (oral LD50 in rats is 9 g/kg). However, certain investigations have shown that it also has an antiviral effect. Azones interact with the lipid domains of the human stratum corneum to exhibit its permeation-enhancing effectiveness..

PYRROLIDONE:

N-methyl-2-pyrrolidone (2P) and 2-pyrrolidone (2P) are the penetration enhancers from this class that are most frequently utilised. Pyrrolidones are frequently employed as penetration enhancers for a variety of medicines, including lipophilic (5-fluorouracil, mannitol, and sulphaguanidine) and hydrophilic (5-hydrocortisone, betamethasone-17-benzoate) ones. Pyrrolidones affect the stratum corneum's and skin's membranous properties through partitioning in the human stratum corneum.

FATTY ACIDS

Long chain fatty acids, of which oleic acid is the most popular, have been proven to increase the penetration of drugs across skin. Drugs that are both hydrophilic and lipophilic have been made to penetrate the skin more readily using fatty acids. Progesterone, acyclovir, estradiol, salicylic acid, and 5-fluorouracil are among the medications whose permeation is aided by fatty acids. Highly lipophilic anti-estrogens are more permeable when they are dissolved in lauric acid. Oleic acid has been shown to boost the penetration of salicylic acid and 5-fluorouracil by 28 and 56 folds, respectively, in an in vitro investigation. The lipid domains in the skin's stratum corneum are altered by fatty acids.

OTHER CATEGORY OF PENETRATION ENHANCERS

By facilitating the polar channel for drug absorption, surfactants improve the penetration of polar medicines. Long hydrocarbon chains that are similar in length aid in the uptake of non-polar or lipophilic medicines.

Two different types of surfactants are employed as penetration boosters.

1.Anionic surfactants, such as decodecylmethly sulphoxide, sodium laurly sulphate, etc., are employed to enhance penetration.

2.Nonionic surfactants such as pluronio F68, pluronic F 127, and others work as penetration enhancers.

II. CONCLUSION

The number of pharmaceuticals that may be administered transdermally may be considerably increased by skin permeation enhancement technology, which is now under research. In 10 years, skin delivery will likely be one of the main methods for drug delivery. Drugs can permeate the skin more efficiently with the help of physical and chemical penetration enhancers, according to research in this area. This publication describes both physical and chemical methods for increasing penetration. Skin irritation should be the primary factor when selecting penetration enhancers in order to have the best enhancing results with the least degree of skin irritation.

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